HHS Public Access

Author manuscript

Thromb Res. Author manuscript; available in PMC 2016 December 01.

Published in final edited form as:

Thromb Res. 2015 December ; 136(6): 1165–1168. doi:10.1016/j.thromres.2015.10.022.

Assessing the intersection of cardiovascular disease, venous thromboembolism, and polycystic ovary syndrome☆

Ekwutosi M. Okoroh[a,*], **Sheree L. Boulet**[b], **Mary G. George**[c], and **W. Craig Hooper**[a]

[a]Division of Blood Disorders, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, 1600 Clifton Rd., N.E., MS-E64, Atlanta, GA 30333, United States

[b]Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, 1600 Clifton Rd., N.E., MS-F74, Atlanta, GA 30333, United States

[c]Division of Heart Disease and Stroke Prevention, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, 1600 Clifton Rd., N.E., MS-F72, Atlanta, GA 30333, United States

Abstract

Introduction—No study has examined how the relationship between polycystic ovary syndrome (PCOS) and atherosclerotic cardiovascular diseases (aCVD), of ischemic stroke (ISCH), acute myocardial infarction (AMI), and peripheral vascular disease (PAD), differ in the presence of venous thromboembolism (VTE).

Materials and methods—We performed a cross-sectional analysis using Truven Health Analytics MarketScan® Commercial databases from 2004–2011. The association between women aged 18–64 years with and without PCOS, and aCVD was assessed using VTE-stratified multivariable logistic regression models.

Results—Overall, women with PCOS were more likely to have aCVD, (aOR, 1.27; 95% CI, 1.10–1.46) especially ISCH (aOR, 1.56; 95% CI, 1.30–1.88), than women without PCOS. When stratified by VTE status, women with PCOS and a VTE diagnosis had a decreased odds of having any aCVD (aOR 0.67; 95% CI, 0.46–0.98), and VTE diagnosis more often preceded the occurrence of ISCH and AMI among women with PCOS compared with women without PCOS.

Conclusions—Overall, women with PCOS were more likely to have aCVD, with stroke being the most prevalent manifestation. Although VTE often occurred before any aCVD, it appeared to have an inverse association with the development of ISCH, AMI, and PAD among women with

☆The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

*Corresponding author at: Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, 1600 Clifton Road Mailstop F74, Atlanta, GA 30333, United States. eokoroh@cdc.gov (E.M. Okoroh).

Disclosure

None of the authors have a conflict of interest.

PCOS, suggesting that aggressively treating VTE or aCVD early may limit the chances of developing the other thrombogenic condition among women with PCOS.

Keywords

Venous thrombosis; Epidemiology; Atherosclerosis; Stroke; Polycystic ovary syndrome

1. Introduction

Atherosclerosis is a chronic and progressive disease that develops early in life [1]. As atherosclerosis progresses, it can lead to the occurrence of cardiovascular events or atherosclerotic cardiovascular diseases (aCVD) the manifestations of which include acute myocardial infarction (AMI), ischemic stroke (ISCH), coronary heart disease, and peripheral vascular disease (PAD) [2,3].

From 2008–2010, the average rate of death attributable to all aCVD was 242.4 per 100,000 [4]. Thus, more than 2200 Americans died of aCVD each day, an average of 1 death every 39 seconds. Similarly, mortality data from2010 indicated that stroke accounted for approximately 1 of every 19 deaths in the U.S. [4]

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting women of reproductive age [5,6]. Its exact etiology is unknown, but it is characterized by a heterogeneous presentation of hyperandrogenism, ovulatory dysfunction, and polycystic ovaries. PCOS has been associated with increased risk for hypertension and metabolic abnormalities (e.g. low levels of high-density lipoprotein cholesterol) [7–10] and women with irregular menses also have manifestations of atherosclerosis, specifically AMI and ISCH, at younger ages [11]. Detection of traditional aCVD risk factors and surrogate markers of atherosclerosis at a young age in women with PCOS puts them at an increased risk for development of symptomatic aCVD [7,10,12].

Studies have likewise shown an association between venous thromboembolism (VTE) and atherosclerosis [13,14]. For example, Prandoni et al. 2003, demonstrated a relationship between asymptomatic atherosclerotic lesions and spontaneous venous thrombosis of the legs [13].

These findings are relevant to women with PCOS because Okoroh et al. 2012 found a higher prevalence of VTE among women with PCOS when compared with the general population [15]. One could infer that women with PCOS and VTE would be at the greatest risk of developing the sequalae of atherosclerosis compared with women without PCOS and with VTE. Thus, the primary aim of this study was to determine how the association between PCOS and aCVD differs in the presence of VTE.

2. Material and methods

2.1. Data source

The data were derived from the 2004–2011 Truven Health Analytics MarketScan® Commercial databases which are longitudinal, de-identified health insurance claims data

from large employers and health plans across the U.S. This commercial database has met or exceeded requirements of the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. The MarketScan databases are de-identified and meet the criteria for a limited-use dataset and does not require specific patient consent for participation in the study [16].

2.2. Study population

Women with PCOS were defined by the presence of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for clinical hyperandrogenism (acne (706.0 or 706.1), alopecia (704.0x), and/or hirsutism (704.1)), ovulatory dysfunction (626.0, 626.1, 626.2, 626.3, 626.4, 626.5, 626.6, 626.7, 626.8, or 626.9), and/or polycystic ovaries (256.4). To reduce misclassification of PCOS cases, we excluded women who met the criteria for PCOS and one or more related conditions: adrenal hyperplasia (255.0 or 255.9), hyperprolactinemia (253.1), or thyroid disorder (244.0, 244.1, 244.2, 244.3, 244.8, 244.9, 242.90, or 242.91). Due to the heterogenic nature of PCOS and its complex presentation and definition, we also looked for the presence of associated conditions seen among women with PCOS (such as obesity [278.0, 278.00–278.02, 783.1, or V77.8]; infertility [628.0 or 628.9]; syndrome X, or metabolic syndrome, [277.7]; hypertension [401.x, 405.x]; thrombophilia [289.81]; and diabetes [250.x]). Diagnoses reported on inpatient claims were considered valid; those based solely on outpatient claims required that the diagnoses be reported on two or more claims that occurred more than 30 days apart.

VTE during the study period was identified using ICD-9-CMcodes for DVT (671.3x, 671.4x, 671.5x, 671.9x, 451.11, 451.19, 451.2, 451.81, 451.9, 453.1, 453.2, 453.40–453.42, 453.8, or 453.9), or PE (673.2x, 673.8x, 415.11, or 415.19), or both, on any inpatient or outpatient claim. We restricted outpatient diagnoses to those who had a filled prescription for an anticoagulant medication within 90 days of the diagnosis; for an inpatient diagnosis, only one ICD-9-CM code for DVT or PE was required.

CVD were defined by the presence of ICD-9-CM codes for ISCH (434.xx; 437.0, 437.1, 437.9; 438.x, and V12.54), AMI (410.xx, excluding 410.x2, which is used to designate follow up to the initial episode) or PAD (443.9).

A unique identifier was used to track women longitudinally over the study period. We included women enrolled for at least 12 months prior to and after the first PCOS diagnosis. The first report of PCOS diagnosis was considered the index date. Those who died during the 12 months after the PCOS diagnosis were also included since the post-index date enrollment restriction would not apply. Women who were not continuously enrolled ≥12 months prior to the index date or ≥12 months following the index date were excluded. Each woman with PCOS was exactly matched with two non-PCOS controls based on age at first PCOS diagnosis for the cases and age at first enrollment for the controls. Controls had to be enrolled for at least 12 continuous months. Cases and controls were restricted to women 18–64 years of age.

2.3. Data analysis

Bivariate analyses with two-tailed chi-square tests were used to compare the distribution of demographic and comorbid factors for women with and without PCOS. Fisher's exact P-values were used to compare the distribution of aCVD between women with and without PCOS. Conditional logistic regression on age was used to assess the likelihood of aCVD diagnosis (ISCH, AMI and PAD) among women with and without PCOS. We stratified the analysis by the presence or absence of a VTE diagnosis. PCOS was diagnosed among the study population before VTE or aCVD was diagnosed. The final models included only those factors that were statistically significant at a priori significance level ($P < .05$) (obesity, diabetes, hypertension, and thrombophilia). All data were analyzed and managed using SAS software version 9.3 (SAS Institute Inc., Cary, NC, USA).

3. Results

The mean age of the study population was 33.4 years. Overall, there were 33 in-hospital deaths among women with PCOS and 99 among the controls. Women with PCOS had significantly higher proportions of all chronic comorbid conditions as well as thrombophilia, infertility, and VTE (Table 1). Of the 1224 women with PCOS and VTE, 529 (43.2%) had a PE. Of the 831 women without PCOS but with VTE, 310 (37.3%) had a PE. Overall, 839 (40.8%) of the study population with VTE had a PE.

Overall, women with PCOS were more likely to have aCVD, (aOR, 1.27; 95% CI, 1.10–1.46) especially ISCH (aOR, 1.56; 95% CI, 1.30–1.88), than women without PCOS. Stratification by VTE is shown in Table 2. Among women with PCOS and VTE, the unadjusted (OR, 0.72; 95% CI, 0.50–1.04) and adjusted (aOR, 0.67; 95% CI, 0.46–0.98) odds of having any aCVD was decreased compared with women without PCOS and with VTE (Table 2). In contrast, women with PCOS and without VTE were more likely to have aCVD diagnosis compared with women without PCOS and without VTE even after adjusting for confounders (Table 2).

Timing of aCVD and VTE occurrence among the study population was also evaluated. VTE tended to precede the occurrence of ISCH and AMI among women with PCOS compared with women without PCOS (Table 3).

4. Discussion

To our knowledge, this is the first study to assess the association between PCOS and aCVD among women with and without VTE. We found that women with PCOS were more likely to have comorbid conditions such as obesity, infertility, and diabetes as well as atherosclerosis manifestations of stroke, myocardial infarction, and peripheral vascular disease compared with women without PCOS. We also found that ischemic stroke was the most likely atherosclerotic manifestation present among this cohort. This finding is similar to the meta-analysis done by de Groot et al. [17] They found a pooled relative risk for coronary heart disease/stroke of 2.02 for women with PCOS compared with those without PCOS.

When stratified by VTE status, we found VTE possibly acting as an effect modifier between aCVD and PCOS where its presence among women with PCOS appeared protective to the occurrence of aCVD. Studies have shown an inverse association between sub-clinical atherosclerosis and future VTE development [18,19]. It is possible that this inverse association may also occur for future development of atherosclerosis after a VTE occurrence. Another plausible reason for our findings is that in situations where VTE occurred before aCVD, the common prothrombotic triggers that both entities share such as thrombogenesis and endothelial damage may have been modified with lifestyle changes (e.g., weight loss) and/or medications (e.g., statins)—thereby decreasing the occurrence of the counterpart disease [13,20]. For example, Chae et al. 2014 found that when angiotensin receptor blockers were given to people who had developed MI or ISCH their chance of developing VTE was reduced [21].

The major strength of this study is in the use of a database that includes a large proportion of the privately-insured U.S. population. Also, the group studied was geographically diverse and included women seen both in an inpatient and an outpatient setting, which offers a better estimate of the prevalence of aCVD, VTE, and PCOS.

4.1. Limitations

Claims databases are comprised of data used for billing rather than for diagnostic purposes, so misclassification of cases may occur due to incomplete or inaccurate coding. To handle misclassification, we applied a restriction to how VTE and aCVD were defined and used an algorithm to define PCOS.

We could not report on the racial makeup of our study population due to lack of demographic information. Also, we did not control for concurrent medications use, such as anticoagulants which may have influenced the protective association we found. As noted earlier, medications use such as statins or angiotensin receptor blockers can improve the likelihood of developing a related thromobogenic condition; it is possible that not controlling for the medication gave us the inverse association seen in this study. In addition, our study only included women less than 65 years which precluded evaluation of aCVD among women whose disease manifests later in life.

5. Conclusion

Our findings add to the limited literature on the relationship between PCOS, VTE and atherosclerosis manifestations such as AMI and stroke. While several studies [8,9,11,22–24] have shown that women with PCOS are more prone to arterial thrombosis, we show here that the story may be more complex when we look at how these three thrombogenic conditions interact with each other. We acknowledge that our findings should be interpreted with caution and the relationship between PCOS and aCVD in the setting of VTE presence should be further evaluated since our data were limited and obtained from administrative claims.

Atherosclerotic manifestations such as ischemic stroke and myocardial infarction have been shown to have a link to VTE, but how PCOS changes this link is unclear. We see that the

presence of VTE among women with PCOS may have an inverse association with the development of atherosclerotic manifestations. Prospective studies will be needed to verify this finding. The implication of our study for clinicians is that aggressive treatment for women with PCOS and venous thromboembolism and women with PCOS and atherosclerotic manifestations may in turn limit their chance of developing the opposite thrombogenic condition in the future.

References

1. Santos RD, Nasir K. Insights into atherosclerosis from invasive and non-invasive imaging studies: should we treat subclinical atherosclerosis? Atherosclerosis. 2009 Aug; 205(2):349–356. Epub 2008 Dec 14. [PubMed: 19281982]
2. Toth PP. Subclinical atherosclerosis: what it is, what it means and what we can do about it. Int. J. Clin. Pract. 2008 Aug; 62(8):1246–1254. (Epub 2008 Jun 28). [PubMed: 18564201]
3. Ohsfeldt RL, Gandhi SK, Fox KM, Bullano MF, Davidson M. Medical and cost burden of atherosclerosis among patients treated in routine clinical practice. J. Med. Econ. 2010; 13(3):500–507. [PubMed: 20673198]
4. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. Heart disease and stroke statistics — 2014 update: a report from the American Heart Association. Circulation. 2014; 129:e28–e292. [PubMed: 24352519]
5. Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. J. Clin. Endocrinol. Metab. 1998 Sep; 83(9):3078–3082. [PubMed: 9745406]
6. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. J. Clin. Endocrinol. Metab. 2004 Jun; 89(6):2745–2749. [PubMed: 15181052]
7. Talbott EO, Zborowski JV, Rager JR, Boudreaux MY, Edmundowicz DA, Guzick DS. Evidence for an association between metabolic cardiovascular syndrome and coronary and aortic calcification among women with polycystic ovary syndrome. J. Clin. Endocrinol. Metab. 2004 Nov; 89(11): 5454–5461. [PubMed: 15531497]
8. Meyer C, McGrath BP, Teede HJ. Overweight women with polycystic ovary syndrome have evidence of subclinical cardiovascular disease. J. Clin. Endocrinol. Metab. 2005 Oct; 90(10):5711–5716. (Epub 2005 Jul 26). [PubMed: 16046590]
9. Carmina E, Chu MC, Longo RA, Rini GB, Lobo RA. Phenotypic variation in hyperandrogenic women influences the findings of abnormal metabolic and cardiovascular risk parameters. J. Clin. Endocrinol. Metab. 2005 May; 90(5):2545–2549. (Epub 2005 Feb 22). [PubMed: 15728203]
10. Wild RA, Carmina E, Diamanti-Kandarakis E, Dokras A, Escobar-Morreale HF, Futterweit W, et al. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. J. Clin. Endocrinol. Metab. 2010 May; 95(5):2038–2049. (Epub 2010 Apr 7). [PubMed: 20375205]
11. Solomon CG, Hu FB, Dunaif A, Rich-Edwards JE, Stampfer MJ, Willett WC, et al. Menstrual cycle irregularity and risk for future cardiovascular disease. J. Clin. Endocrinol. Metab. 2002 May; 87(5):2013–2017. [PubMed: 11994334]
12. Shroff R, Kerchner A, Maifeld M, Van Beek EJ, Jagasia D, Dokras A. Young obese women with polycystic ovary syndrome have evidence of early coronary atherosclerosis. J. Clin. Endocrinol. Metab. 2007 Dec; 92(12):4609–4614. (Epub 2007 Sep 11). [PubMed: 17848406]
13. Prandoni P, Bilora F, Marchiori A, Bernardi E, Petrobelli F, Lensing AW, et al. An association between atherosclerosis and venous thrombosis. N. Engl. J. Med. 2003; 348:1435–1441. [PubMed: 12686699]
14. Becattini C, Agnelli G, Prandoni P, Silingardi M, Salvi R, Taliani MR, et al. A prospective study on cardiovascular events after acute pulmonary embolism. Eur. Heart J. 2005; 26:77–83. [PubMed: 15615803]

15. Okoroh EM, Hooper WC, Atrash HK, Yusuf HR, Boulet SL. Is polycystic ovary syndrome another risk factor for venous thromboembolism? United States, 2003–2008. Am. J. Obstet. Gynecol. 2012 Nov; 207(5):377, e1–e8. http://dx.doi.org/10.1016/j.ajog.2012.08.007 (Epub 2012 Aug 10). [PubMed: 22959762]

16. Hansen LG, Chang S. Health Research Data for the Real World: The MarketScan® Databases. Truven Health Analytics. 2011 Jul.

17. de Groot PC, Dekkers OM, Romijn JA, Dieben SW, Helmerhorst FM. PCOS, coronary heart disease, stroke and the influence of obesity: a systematic review and meta-analysis. Hum. Reprod. Update. 2011 Jul-Aug;17(4):495–500. http://dx.doi.org/10.1093/humupd/dmr001 (Epub 2011 Feb 18). [PubMed: 21335359]

18. Reich LM, Folsom AR, Key NS, Boland LL, Heckbert SR, Rosamond WD, et al. Prospective study of subclinical atherosclerosis as a risk factor for venous thromboembolism. J. Thromb. Haemost. 2006 Sep; 4(9):1909–1913. (Epub 2006 Jul 12). [PubMed: 16836659]

19. van der Hagen PB, Folsom AR, Jenny NS, Heckbert SR, O'Meara ES, Reich LM, et al. Subclinical atherosclerosis and the risk of future venous thrombosis in the Cardiovascular Health Study. J. Thromb. Haemost. 2006 Sep; 4(9):1903–1908. [PubMed: 16961598]

20. Sørensen HT, Horvath-Puho E, Pedersen L, Baron JA, Prandoni P. Venous thromboembolism and subsequent hospitalisation due to acute arterial cardiovascular events: a 20-year cohort study. Lancet. 2007 Nov 24; 370(9601):1773–1779. [PubMed: 18037081]

21. Chae YK, Khemasuwan D, Dimou A, Neagu S, Chebrolu L, Gupta S, et al. Inhibition of renin angiotensin axis may be associated with reduced risk of developing venous thromboembolism in patients with atherosclerotic disease. PLoS One. 2014 Jan 31.9(1):e87813. http://dx.doi.org/10.1371/journal.pone.0087813. eCollection 2014. [PubMed: 24498202]

22. Birdsall MA, Farquhar CM, White HD. Association between polycystic ovaries and extent of coronary artery disease in women having cardiac catheterization. Ann. Intern. Med. 1997 Jan 1; 126(1):32–35. [PubMed: 8992921]

23. Shaw LJ, Bairey Merz CN, Azziz R, Stanczyk FZ, Sopko G, Braunstein GD, et al. Postmenopausal women with a history of irregular menses and elevated androgen measurements at high risk for worsening cardiovascular event-free survival: results from the National Institutes of Health–National Heart, Lung, and Blood Institute sponsored Women's Ischemia Syndrome Evaluation. J. Clin. Endocrinol. Metab. 2008 Apr; 93(4):1276–1284. http://dx.doi.org/10.1210/jc.2007-0425 (Epub 2008 Jan 8). [PubMed: 18182456]

24. Talbott EO, Guzick DS, Sutton-Tyrrell K, McHugh-Pemu KP, Zborowski JV, Remsberg KE, et al. Evidence for association between polycystic ovary syndrome and premature carotid atherosclerosis in middle-aged women. Arterioscler. Thromb. Vasc. Biol. 2000 Nov; 20(11):2414–2421. [PubMed: 11073846]

Table 1

Characteristics of women with and without polycystic ovary syndrome.

Factors	PCOS		No PCOS		P-value
	N = 125,268	%	N = 250,536	%	
Age categories (years)					
18–24	22,218	17.7	44,434	17.7	1.0
25–34	49,462	39.5	98,924	39.5	
35–44	36,523	29.2	73,048	29.2	
45–54	15,532	12.4	31,064	12.4	
55–64	1,533	1.2	3,066	1.2	
Comorbidities					
Metabolic syndrome	1,365	1.1	324	0.1	<.0001
Obesity	9,688	7.7	5,582	2.2	<.0001
Delivery	28,682	22.9	20,861	8.3	<.0001
Diabetes	5,739	4.6	4,762	1.9	<.0001
Hypertension	14,693	11.7	12,588	5.0	<.0001
Thrombophilia	451	0.4	242	0.1	<.0001
Infertility	4,526	3.6	1,299	0.5	<.0001
VTE	1,224	1.0	831	0.33	<.0001

PCOS, polycystic ovary syndrome; VTE, venous thromboembolism.

Table 2

Association between PCOS, no PCOS and aCVD, by VTE status.

Variables	PCOS		No PCOS		OR	95% CI	aOR[a]	95% CI
	N	%	N	%				
VTE = yes								
Any aCVD	68	5.56	60	7.22	0.72	0.50–1.04	0.67	0.46–0.98
ISCH	35	2.86	31	3.73	0.73	0.44–1.21	0.66	0.38–1.70
AMI	15	1.81	8	0.65	0.34	0.14–0.81	0.35	0.14–0.87
PAD	28	2.29	18	2.17	1.04	0.57–1.92	1.03	0.56–1.90
VTE = no								
Any aCVD	372	0.30	372	0.15[b]	2.02	1.75–2.34	1.28	1.11–1.49
ISCH	233	0.19	187	0.07[b]	2.52	2.08–3.05	1.63	1.23–2.13
AMI	122	0.10	153	0.06[b]	1.61	1.29–2.04	1.02	0.80–1.31
PAD	28	0.02	48	0.02	1.18	0.74–1.88	0.65	0.40–1.05

PCOS, polycystic ovary syndrome; aCVD, atherosclerotic cardiovascular diseases; VTE, venous thromboembolism; ISCH, ischemic stroke; AMI, acutemyocardial infarction; PAD, peripheral vascular disease.

[a] All models adjusted for obesity, diabetes, hypertension, and history of thrombophilia.

[b] P value < 0.01.

Table 3

Timing of aCVD and VTE occurrences among women with and without polycystic ovary syndrome.

aCVD Outcome	N (total)	PCOS		N (total)	No PCOS		Fisher's exact P value
		Occurred before VTE (%)	Occurred after VTE (%)		Occurred before VTE (%)	Occurred after VTE (%)	
Ischemic stroke	35	48.6	51.4	31	77.4	22.6	0.02
Acute myocardial infarction	8	37.5	62.5	15	80.0	20.0	0.07
Peripheral vascular disease	28	57.1	42.9	18	77.8	22.2	0.21
Any aCVD	68	48.5	51.5	60	76.7	23.3	0.002

aCVD, atherosclerotic cardiovascular disease; VTE, venous thromboembolism; PCOS, polycystic ovary syndrome.